Systematic Review

Effect of Coenzyme Q10 Supplementation on Diabetes Biomarkers: a Systematic Review and Meta-analysis of Randomized Controlled Clinical Trials

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Abstract

Background: Several studies have investigated the effect of Co-Q10 on diabetes biomarkers, but findings are inconsistent. This systematic review and meta-analysis of clinical trials was conducted to summarize the effect of Co-Q10 supplementation on diabetes biomarkers.

Methods: We searched Pubmed, EMBASE, Science direct, ISI web of science, and Google Scholar for randomized controlled trials from 1989 until March 2016. We included randomized controlled trials reporting fasting blood glucose (FBG), fasting insulin and HbA1c. In total, we found 16 articles that examined the effect of Co-Q10 on fasting blood glucose, fasting insulin and HbA1c. Mean ± standard deviations (SD) of defined outcomes were used for calculating standardized mean differences (SMD) and its 95% confidence interval (95%CI) between intervention and control treatments based on Hedges' estimator.

Results: Our preliminary meta-analysis on 14 eligible studies regarding the effect of Co-Q10 supplementation on FBG indicated a slightly significant decrement (SMD:-0.28 mg/d; 95% CI: -0.12, 0.04), with a substantial between-study heterogeneity (Cochrane Q test, $I^2 = 93.9\%$, $P < 0.0001$). After removal of three studies, heterogeneity was eliminated and a slightly significant decrease was found in FBG (SMD: -0.20 mg/dL, 95% CI: -0.38, -0.02). The effect of Co-Q10 on HbA1c and fasting insulin was not significant. SMDs for the effect of Co-Q10 on HbA1c and fasting insulin were -0.05% (95% CI: -0.22, 0.12) and 0.12 pmol/L (95% CI: -0.21, 0.44), respectively.

Conclusion: Co-Q10 supplementation slightly but significantly reduced fasting blood glucose, but not fasting insulin and HbA1c. More long-term studies are necessary to examine the association between Co-Q10 supplementation and diabetes biomarkers.

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Keywords: Co-Q10, fasting blood glucose, fasting insulin, glycemic control, HbA1c diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a common health problem affecting approximately 8.3% of the world population which seems to increase in the next 20 years.[1] Poor glycemic control will cause long-term adverse outcomes in T2DM subjects, including microvascular and macrovascular complications, such as cardiovascular events, renal failure, blindness and peripheral neuropathy.[2] Several studies have noted that hyperglycemia is associated with enhanced oxidative stress and impaired insulin secretion. Appropriate management of hyperglycemia is thought to reduce morbidity and the number of complications associated with T2DM.[3,4]

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Recently, increasing effort has been devoted to identify dietary factors that can delay the onset, or progression of diabetes. While the classic essential nutrients have been widely studied in this regard, there is also great interest in the evaluation of Co-Q10.[5]

Co-Q10 is a chief component of mitochondrial oxidative phosphorylation and adenosine triphosphate production.[6,7] This vitamin-like compound, which is similar to vitamin K, is responsible for three known biologic functions. It increases mitochondrial adenosine triphosphate (ATP) energy production, provides potent antioxidant effects, and enhances cell membrane stabilization.[8–10]

Diabetic individuals might have Co-Q10 deficiency. This occurs due to the diabetic diet, statin intake and inappropriate intestinal absorption as well as lower endogenous production. Thus, it is reasonable to postulate that, antioxidants such as Co-Q10 may have beneficial effects on diabetes biomarkers such as HbA1c, fasting insulin and fasting blood glucose.

To date, a close association has been hypothesized between T2DM and Co-Q10 deficiency. Some studies have revealed that Co-Q10 improves the clinical diabetes biomarkers of diabetes.[11,12] However, some investigators have failed to find such effects.[13,15] Therefore, the results of these controlled trials have been inconsistent regarding the effect of Co-Q10 supplementation on diabetes biomarkers.[11–15]

These discrepancies might be related to the differences of studies

in terms of population and duration of studies. Despite several controlled trials, we are aware of no systematic review and meta-analysis of clinical trials on this subject. This meta-analysis was conducted to summarize the available literature of randomized controlled trials to assess the effect of Co-Q10 supplementation on changes in HbA1c, fasting blood glucose and fasting insulin in comparison with placebo group in healthy and unhealthy subjects.

Materials and Methods

Search strategy

We searched for articles that were published before March 2016 in ScienceDirect (www.sciencedirect.com/science/journals) Proquest (www.proquest.com), MEDLINE (www.pubmed.com) and Google Scholar (scholar.google.com) databases. Key words such as "Coenzyme Q10", "ubiqinone Q10", "ubiquinol", "CoQ10" combined with "glycemic control", "blood sugar", "Hemoglobin A1c", "HbA1C","Hb A1C", "Glycated hemoglobin", "Hemoglobin A1c", "Glycosylated Hemoglobin A", "glycohemoglobin A", "glucose tolerance"," blood insulin", "diabetes mellitus", "energy density" , "energy-density", "energy dense", "calorie density", "caloric density", "calorie dense", "energy concentration" and "calorie concentration" were used in the primary search strategy and in a subsequent medical subheading (MESH) terms search.

Study selection

Totally, 660 studies were identified that evaluated the effect of Co-Q10 on diabetes and its biomarkers. Potentially relevant studies were selected based on the following inclusion criteria: 1) single-group intervention and randomized controlled trials with either a parallel or a crossover design; 2) exact amounts of fasting blood glucose, fasting insulin and HbA1c. Studies included in the meta-analysis were those that had available results in a form that could be used for the present analysis. Exclusion criteria were as follows: 1) trials with abstract only and trials with no report of exact amounts of the needed biomarkers (n = 3); 2) review, cross sectional and cohort studies (n = 5) and 3) studies written in a language other than English (n = 2). Of the initial 660 studies that were extracted from the search machine, 600 were irrelevant to our topic of meta-analysis just on the basis of title and abstract. Of the remaining 60 studies, 44 were excluded. The flow diagram of study selection process is shown in Figure 1.

Data extraction

The following characteristics were extracted from the original reports by 2 independent reviewers: design of the study (randomized parallel, randomized crossover, or non-randomized crossover intervention trial), surname of lead author, year of publication, sample size, participants' mean age and gender, study duration, and the inclusion and exclusion criteria. The

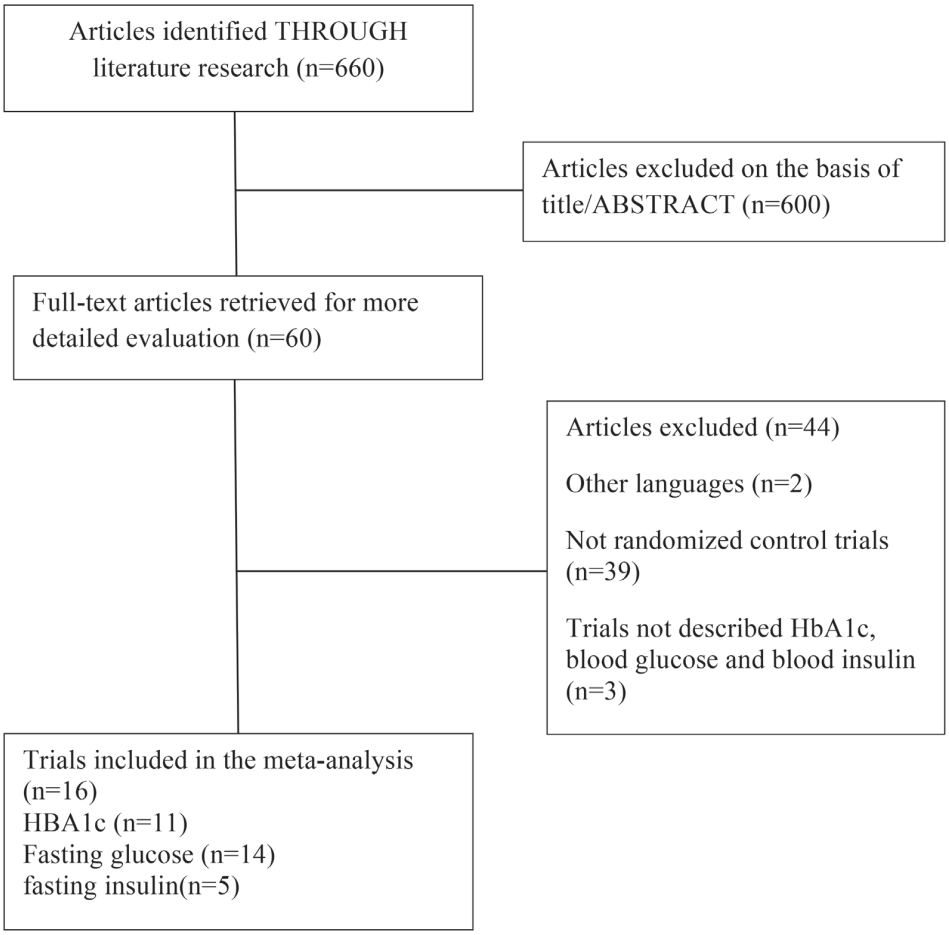

Figure 1. Flow diagram of the process of article selection for meta-analysis.

Table 1. Characteristics of trials included in the meta-analysis.

Author (publication year)	Subjects(n) Intervention/ Control gender	Design	Duration (weak)	Co-Q10 dose	Presented data	Notes about subjects	- Overall effect for intervention and control respectively	
Chew, et al[28] 2008	18/18 both	Cross-over	25	200 (mg/day)	HbA1c FBG[§]	With type 2 diabetes with left ventricular diastolic dysfunction	FBG	Q10: 2 ± 19.7 Control: 3 ± 19.4
							HbA1c	Q10: -0.1 ± 0.7 Control: -0.1 ± 0.8
Dai, et al[30] 2011	28/28 both	Parallel	8	300 (mg/day)	HbA1c FBG	Patients with CAD[§]	FBG	Q10: 6.3 ± 23 Control: 8.5 ± 36
							HbA1c	Q10: -0.13 ± 0.48 Control: .06 ± 0.97
Erikson, et al[14] 1999	28/28 both	Parallel	25	100 (mg/day)	HbA1c FBG	Type 2 diabetes	FBG	Q10: -12 ± 112 Control:-12 ± 76
							HbA1c	Q10: 0.4± 5.2 Control: 0.2± 2.4
Hamilton, et al[24] 2009	23/23 NR	Cross-over	12	200 (mg/day)	HbA1c	Type 2 diabetes	HbA1c	Q10: -0.1 ± 0.48 Control: 0.1 ± 0.48
Henrikson, et al[15] 1999	17/17 both	Parallel	12	200 (mg/day)	HbA1c FBG insulin	Type 1 diabetes	HbA1c	Q10: -0.18 ± 0.73 Control: 0.18 ±0.73
							FBG	Q10: -15 ± 21 Control: -8 ± 20.7
							Insulin	Q10: 0 ± 40.5 Control: 4 ± 65
Hodgson, et al[25] 2002	19/18 both	Parallel	12	200 (mg/day)	HbA1c FBG insulin	Type 2 diabetes and dyslipidemia	HbA1c	Q10: 0.1 ± 1.13 Control: 0.3 ± 1
							FBG	Q10: -6 ± 32 Control: 4 ± 27.7
							Insulin	Q10: 12 ± 27 Control: 0 ± 30
Ikematsu, et al[22] 2006	22/20 both	Parallel	8	600 (mg/day)	FBG	Type 2 diabetes	FBG	Q10: 4.8 ± 1.4 Control: -0.1 ± 1.2
Kolahdooz, et al[31] 2013	31/33 both	Parallel	12	200 (mg/day)	HbA1c FBG	Type 2 diabetic patients	HbA1c	Q10: -0.61± 2.09 Control: -0.17± 1.8
							FBG	Q10: 0 ± 22 Control: 8 ± 19.6
Lim, et al[12] 2008	40/40 both	Parallel	12	200 (mg/day)	HbA1c FBG	Type 2 diabetes	HbA1c	Q10: 0.2 ± 1.06 Control: 0 ± 0.1
							FBG	Q10: 0 ± 24.1 Control: -2.4 ± 23.4
Mori, et al[29] 2009	18/18 both	Parallel	8	200 (mg/day)	FBG insulin	Chronic renal impairment	FGB	Q10: 3 ± 8.4 Control: 0 ± 7
							Insulin	Q10: 7 ± 24.5 Control: -1 ± 18.3
Playfold, et al[20] 2003	20/20 both	Parallel	12	200 (mg/day)	HbA1c	Type 2 diabetes and dyslipidemia	HbA1c	Q10: 0.1±1.45 Control: 0.3 ± 0.99

Shargorodsky, et al[23] 2010	36/34 both	Parallel	25	120 (mg/day)	HbA1c FBG	Patients with at least two cardiovascular risk factors	HbA1c	Q10: -0.75 ± 1.8 Control: 0.79 ± 1.3
							FBG	Q10: 2 ± 37 Control: 4.3 ± 32
Mohammed-jawad, et al[26] 2014	19/19 both	Parallel	8	150 (mg/day)	HbA1c FBG	Type2 diabetes	HbA1c:	Q10: -1.1 ± 0.9 Control: -0.4 ± 3.7
							FBG:	Q10: -42 ± 47 Control: 10 ± 31
Singh, et al[13] 1999	30/28 both	Parallel	8	120 (mg/day)	FBG insulin	Hypertensive patients with CAD	FBG	Q10: -46.4 ± 12.5 Control: -11 ± 10.7
							Insulin	Q10: -208 ± 25.5 Control: -39 ± 22.5
Singh, et al[21] 1999	25/22 both	Parallel	4	120 (mg/day)	FBG	Acute coronary disease	FBG	Q10: -21.3 ± 7 Control: -1 ± 1.7
Yubero-Serrano, et al[27] 2010	20/20 both	Cross-over	4	200 (mg/day)	FBG insulin	Healthy	FBG	Q10: -12.7 ± 22.5 Control: -2.7 ± 7.2
							Insulin	Q10: -13.8 ± 86.2 Control: 6.24 ± 110

§ FBG = fasting blood glucose, CAD = coronary artery disease.

required outcome measures included the net changes in plasma concentrations of glycated hemoglobin (HbA1c) in percent, fasting blood glucose in mg/dL, and fasting insulin concentrations in Pmol/L after Co-Q10 supplementation. Mean ± SD of fasting blood glucose, fasting insulin, and HbA1c, for intervention and control groups after intervention period were presented by most of the studies while some studies did not report the exact amount. The characteristics of the trials are listed in Table 1.

Data synthesis and meta-analyses

When at least three publications with homogenous outcome(s) existed, meta-analysis was performed.[11,13,15] Mean standard deviations (SD) of proposed outcomes were used for calculating mean differences. For each study, Hedges' estimator was used to approximate the population standardized mean differences (SMD) and its 95% confidence interval (95% CI) between intervention and control treatments (i.e. difference of population means in the two treatments was divided by the population standard deviation of the means difference).

Within and between-study heterogeneities were assessed using Cochran's Q-statistics,[16] and the heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I square,[17,18] that provides a measure of the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance. I^2 values range between 0 and 100%, and I^2 values of 25%, 50% and 75% are referred to as low, moderate, and high estimates, respectively.[16] As we found no evidence of heterogeneity, the fixed effect method[18] otherwise random effect or Meta regression were conducted. The funnel plot, Begg and Mazumdar rank correlation test and Egger's test were employed to assess publication bias.[19] Also, subgroup analyses were conducted to explore their potential heterogeneity. Sensitivity analysis was conducted to explore the extent to which inferences might depend on a particular study or number of publications. Statistical analyses were conducted using Stata version 11.2 (Stata Corp, College Station, TX). *P*-values less than 0.05 were considered statistically significant.

Results

Findings from systematic review

The current systematic review identified 16 controlled trials that addressed the effect of Co-Q10 supplementation on diabetes' biomarkers. The included studies had a total of 920 participants aged 35–70 y with a BMI range of 23 to 31.

We included controlled clinical trials, either cross-over or parallel design, in the present meta-analysis.[12,13,20–25] Fourteen of all 16 studies which met our inclusion criteria had assessed the effect of Co-Q10 on fasting blood glucose. Significant reduction in fasting blood glucose was observed in 5 studies after Co-Q10 supplementation.[13,21,22,25,26] However, the other studies found no significant effect.[12,14,15,23,27–30] Five studies were identified that examined the effect of Co-Q10 on fasting insulin. One study reported a significant decrement in fasting insulin by administrating Co-Q10 [13]; nevertheless, the others indicated no significant changes.[15,25,27,29] HbA1c was examined in 10 studies and only 4 showed significant reduction in HbA1c after consumption of Co-Q10[12,20,25,31]; while the other 6 investigations revealed no significant impact.[14,15,23,24,28,30]

Other supplements affecting glycemic biomarkers were also prescribed in some researches. For example, other antioxidants like vitamin C, vitamin E and selenium were prescribed beside Co-Q10 in three studies.[23,29] Results from these investigations did not confirm the beneficiary effect of Co-Q10 on fasting blood glucose and HBA1c.[23,29]

Moreover, participants in 10 studies received medicine beside Co-Q10. In 3 out of 10 studies, HbA1c and fasting blood glucose decreased significantly by consuming Co-Q10.[13,20,21] Whilst some investigations were performed on healthy subjects, others were done on subjects with various metabolic disorders such as diabetes mellitus,[12,14,15,23,28,31] dyslipidemia,[20,23,25] cardiovascular disease[21,13,28,30] or renal disorders.[29]

Given the importance of duration and dose of Co-Q10 supplementation, we also considered these two variables in all included studies. The daily dose of Co-Q10 ranged from 100 to 900 mg/d and the mean of daily dose was 260 mg in the publications.

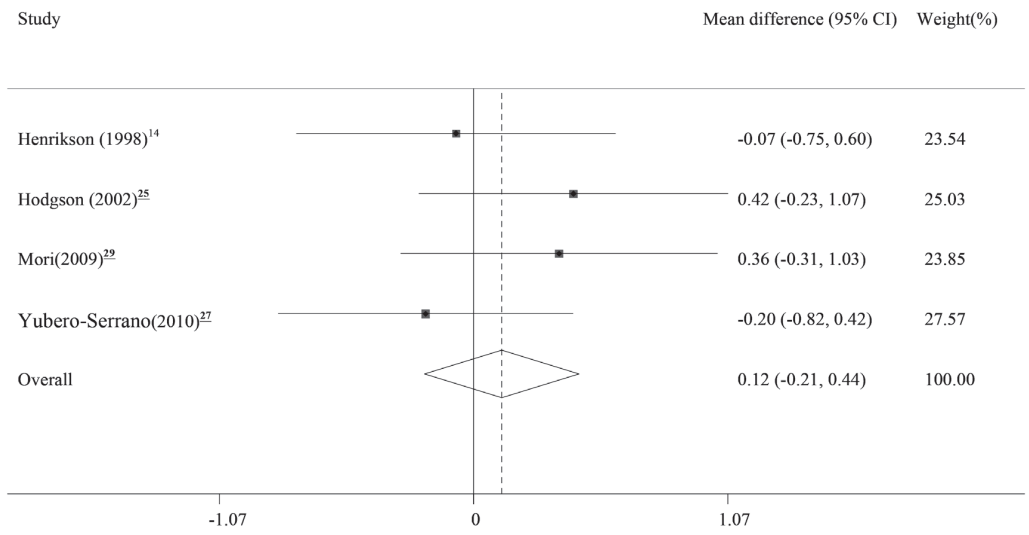

Figure 2. Forest plot of randomized controlled trials illustrating weighted mean difference in fasting insulin between the Co-Q10-supplemented and control groups for all eligible studies.

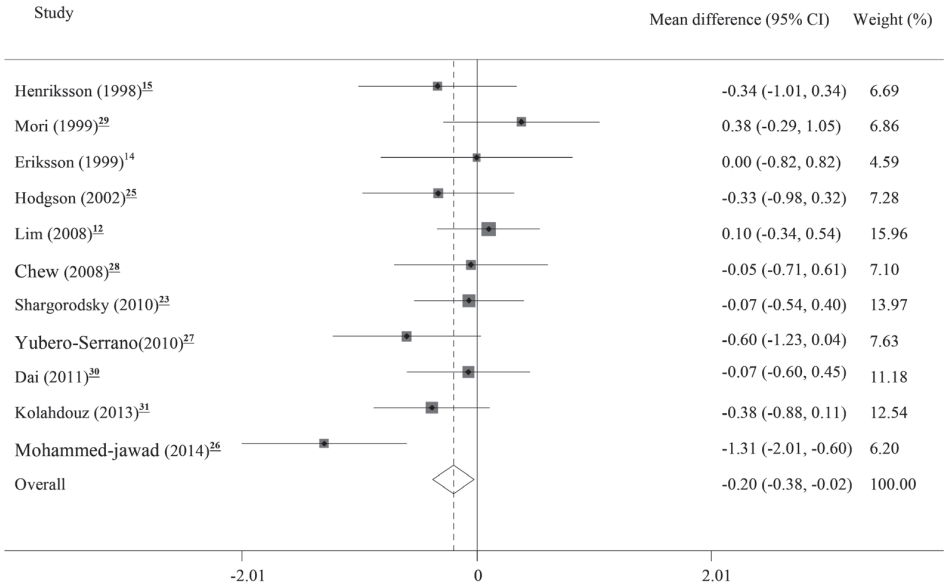

Figure 3. Forest plot of randomized controlled trials illustrating weighted mean difference in fasting blood glucose (FBG) between the Co-Q10-supplemented and control groups for all eligible studies.

Furthermore, the duration of Co- Q10 supplementation was quite different between studies, ranging from 4 to 25 weeks, and the mean of duration was 11 weeks. It should be noted that the primary aim of most of the studies was not evaluating diabetes indicators.[22,28,30]

Findings from meta-analysis

The results of the meta-analysis on five studies regarding supplementation with Co-Q10 showed no significant effect on fasting insulin (SMD: -0.26 pmol/L, 95% CI: -0.57, 0.06). However, an evident heterogeneity was revealed among studies (Cochrane Q test, $I^2 = 96.8\%$, $P < 0.001$). To investigate the source of heterogeneity, we performed subgroup analysis based on health status of study participants (healthy or unhealthy), diseases (diabetes type 2, heart diseases, dyslipidemia), duration of intervention (>5 weeks or < 5 weeks) and dose of supplements (<200 mg/day or >200 mg/day). Nevertheless, we could not eliminate heterogeneity in any of the mentioned subgroup analyses.

Hence, to further explore for the source of heterogeneity, we performed sensitivity analysis. Removal of the study by Singh *et al.* eliminated the heterogeneity among the studies (Cochrane Q test, $I^2 = 0.0\%$, $P = 0.445$).[13] By removing the said study, the association between Co-Q10 supplementation and fasting insulin did not change substantially (0.12 pmol/L, 95%: -0.21, 0.44)[13] (Figure 2).

Our preliminary meta-analysis on 14 eligible studies regarding the effect of Co-Q10 supplementation on fasting blood glucose

Table 2. Effect of Co-Q10 on fasting blood glucose, insulin and HbA1c in different subgroups.

Pooled variable	Categorized by	Subgroups (number of effect size in each subgroup)	Effect size	95% CI	P	I-squared	P for heterogeneity	P for between subgroup heterogeneity
HbA1c								
	Diabetes	Yes	-0.025	-0.256, 0.207	0.550	0.0%	0.834	0.735
		No	-0.085	-0.34, 0.121	0.978	0.0%	0.520	
	Cardiovascular	Yes	-0.101	-0.435, 0.234	0.775	0.0%	0.556	0.738
		No	-0.034	-0.235, 0.167	0.854	0.0%	0.741	
	Dyslipidemia	Yes	-0.076	-0.405, 0.252	0.836	0.0%	0.648	0.862
		No	-0.042	-0.245, 0.160	0.830	0.0%	0.684	
	Medicine use	Yes	-0.013	-0.205, 0.179	0.926	0.0%	0.895	0.371
		No	-0.212	-0.603, 0.180	0.925	0.0%	0.289	
	Health status	Un-healthy	-0.060	-0.243, 0.122	0.870	0.0%	0.517	0.776
		Healthy	0.020	-0.500, 0.539	0.928	0.0%	0.941	
	Duration	<20 weeks	-0.076	-0.275, 0.123	0.814	0.0%	0.454	0.628
		>20 weeks	0.022	-0.323, 0.368	0.996	0.0%	0.899	
	Intervention dose	<200 mg/day	-0.042	-0.348, 0.264	0.899	0.0%	0.788	0.940
		>200mg/day	-0.056	-0.265, 0.153	0.764	0.0%	0.599	
Blood glucose								
	Diabetes	Yes	-0.209	-0.434, 0.017	0.028	60.2%	0.070	0.905
		No	-0.187	-0.465, 0.091	0.292	19.2%	0.188	
	Cardiovascular	Yes	-0.064	-0.474, 0.345	0.0%	0.960	0.758	0.473
		No	-0.230	-0.424, -0.037	0.030	53.0%	0.020	
	Dyslipidemia	Yes	-0.157	-0.537, 0.223	0.519	0.0%	0.419	0.801
		No	-0.212	-0.409, -0.014	0.030	53.1%	0.036	
	Other supplements	Yes	0.081	-0.303, 0.465	0.282	13.6%	0.678	0.106
		No	-0.274	-0.471, -0.077	0.088	41.9%	0.006	
	Medicine use	Yes	-0.165	-0.381, 0.051	0.055	51.3%	0.135	0.587
		No	-0.267	-0.566, 0.032	0.178	39.0%	0.080	
	Dose	<200mg/day	-0.358	-0.671, -0.046	0.027	67.4%	0.025	0.230
		³200 mg/day	-0.127	-0.339, 0.084	0.331	13.0%	0.238	
	Duration	<20weeks	-0.222	-0.409, -0.036	0.030	53.1%	0.019	0.492
		>20weeks	-0.031	-0.544, 0.481	0.924	0.0%	0.905	

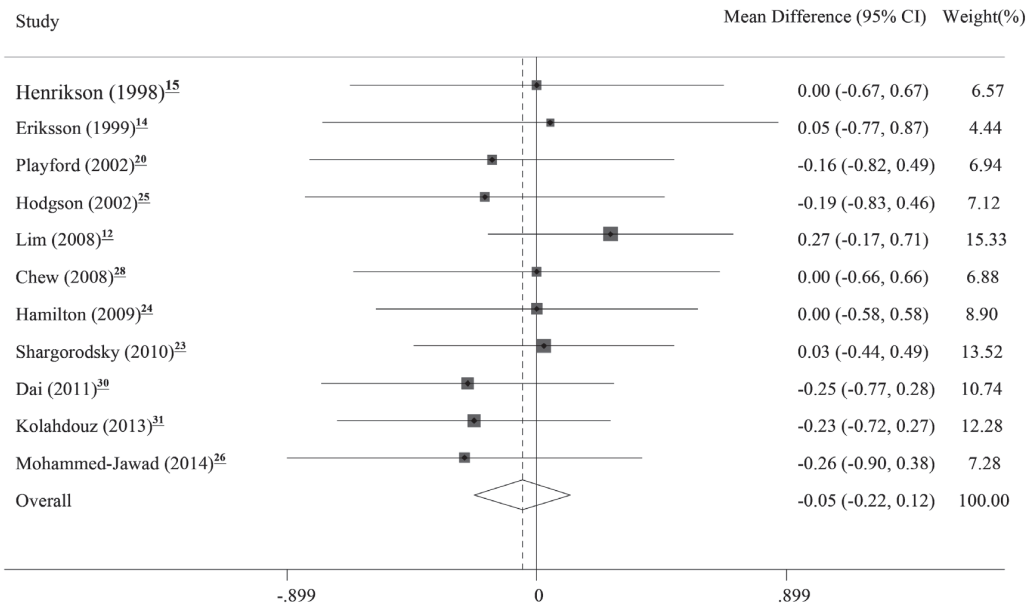

Figure 4. Forest plot of randomized controlled trials illustrating weighted mean difference in HbA1c between the Co-Q10-supplemented and control groups for all eligible studies.

among 710 subjects indicated that the pooled standardized mean difference of glucose was -0.28 mg/d (95% CI: -0.12, 0.04). However, there was substantial between-study heterogeneity (Cochrane Q test, $I^2 = 93.9\%$, $P < 0.0001$). To find the source of heterogeneity, we performed subgroup analyses. However, the heterogeneity remained significant within studies. Between-study heterogeneity moderately disappeared by removal of three studies (Cochrane Q test, $I^2 = 43.0\%$, $P = 0.063$).[13,21,22] Furthermore, after removal of the three studies, the clinical significance of a reduction of fasting glucose was 0.2 mg/dL (-0.20 mg/dL, 95%: -0.38, -0.02) (Figure 3), which is unknown and is apt to be of little clinical benefit .

We performed subgroup analysis based on diseases, during of intervention, dose of intervention, supplement use and medicine use to remove the heterogeneity. However, heterogeneity remained significant in all subgroup analyses. Table 2 represents the effect of Co-Q10 supplementation on variables such as fasting blood glucose, insulin and HbA1c based on different subgroup analyses.

The analysis of data on 11 studies that assessed HbA1c indicated that Co-Q10 supplementation could not decrease the HbA1c. The overall pooled standardized mean difference was -0.05% (95% CI: -0.22, 0.12). No heterogeneity was found between studies (Cochrane Q test, $I^2 = 0.0\%$, $P = 0.95$) (Figure 4).

Publication bias

Despite a slight asymmetry in Begg's funnel plot, we did not find any evidence of publication bias for insulin (Egger's test, $P = 0.511$), fasting blood glucose (Egger's test, $P = 0.345$) or HbA1c (Egger's test, $P = 0.359$**)**.

Discussion

Findings from the present meta-analysis indicated that Co-Q10 supplementation does not reduce diabetes biomarkers significantly. Since there was significant heterogeneity among studies for biomarkers such as fasting insulin and fasting blood glucose, the results did not represent exact valurd. By performing subgroup analysis, the heterogeneity among studies did not disappear. We could remove heterogeneity by removing 3 out of 14 studies which assessed the effect of Co-Q10 on glucose levels.[13,21,22] Furthermore, we removed the heterogeneity by omitting 1 out of 5 studies which examined the effect of Co-Q10 on insulin levels.[13] By removing the heterogeneity, no changes were found in results. The results of our meta-analysis revealed that Co-Q10 supplementation slightly but significantly reduced fasting blood glucose, but not fasting insulin and HbA1c. High doses of Co-Q10 intake (900 mg/day) and intake of supplements other than Co-Q10 were the most important reasons for omitting the studies in order to remove the heterogeneity.

Few epidemiologic studies have investigated the effects of Co-Q10 on glycemic control. In a research by Folkers K *et al*., higher serum Co-Q10 was associated with lower HbA1c cross-sectionally.[32] This is in contrast with the results of a research by Menke T *et al*., which revealed that serum Co-Q10 concentration was higher in patients with poor control than those with good control.[33]

The results of controlled intervention studies in humans are inconsistent.[14,15,20] Singh *et al.* found a significant reduction in fasting blood glucose and fasting insulin with Co-Q10 supplementation (120 mg per day) in diabetic hypertensive subjects. Consistently, Mohammed-Jawad *et al.* showed that supplementation with Co-Q10 at a dose of 75 mg and in combination with oral anti-diabetic drugs reduced fasting blood glucose and HbA1c after 8 weeks of intervention.[26] However, some investigators did not observe any lowering effect of Co-Q10 on fasting blood glucose and fasting insulin[29] or HbA1c in 23 type 2 diabetic subjects who received 200 mg per day Co-Q10 or placebo for 6 months.[15] Moreover, in 34 type 1 diabetic subjects who received100 mg per day Co-Q10 or placebo for 3 months, Co-Q10 did not improve HbA1c.[20]

It should be noted that HbA1c is known as a long-term indicator

of glycemic control. Therefore, a short duration of treatment is unlikely to cause an improvement in HbA1c. This might be the reason why some studies did not observe any lowering effect of Co-Q10 supplementation on HbA1c levels.[15,30]

It should be kept in mind that this is not the only property proposed for Co-Q10. Supplementation with this vitamin-like substance could also improve hypertension and coronary artery disease.[13] Furthermore, Co-Q10 could have a cardio-protective effect.[34] Some investigators found that Co-Q10 supplementation can decrease blood pressure in subjects with uncontrolled or poorly controlled hypertension.[35,36] A study on 76 older men and women with isolated systolic hypertension showed a significant fall in systolic blood pressure of 18 mmHg. Moreover, Co-Q10 supplementation appeared to improve macro-vascular endothelial function.[37]

Although 200 mg of Co-Q10 per day for 12 weeks in type 2 diabetics led to improvement in blood pressure and endothelial function, no improvement in oxidative stress was observes as measured by plasma F(2) isoprostanes.[21] However, another research found that 120 mg of Co-Q10 over an 8-week time period in 30 patients with coronary artery disease significantly decreased oxidative stress.[14]

Increasing evidence suggests that individuals with type 2 diabetes are under greater oxidative stress.[38,39] Oxidative stress and hyperglycemia may be causally related. Moreover, oxidative stress contributes to and also results from hyperglycemia, insulin resistance and malfunction in *B*-cell function.[40,41] This provides a theoretical basis for investigation of the effects of Co-Q10 on glycemic control in diabetic patients. The exact mechanisms of how oxidative stress causes hyperinsulinemia are not known. *B*-cells of the pancreas are very susceptible to damage because of the poor endogenous antioxidant enzyme system. Co-Q10 is also a component of beta cells and liver. The beta cells function, glucose and fatty acid metabolism in the liver may be deteriorated in deficiency of Co-Q10, vitamin A, E and C and beta-carotene, resulting in impaired insulin action and hyperinsulinemia. Therefore, treatment with Co-Q10 may provide protection to beta cells of the pancreas, liver and endothelial cells, resulting in improved cell metabolism and insulin action.

Between-study heterogeneity was significant in articles evaluating the effect of Co-Q10 supplementation on fasting blood glucose and fasting insulin. Although we could attenuate some of the observed heterogeneity through several subgroup analyses, the heterogeneity persisted in all cases. Several subgroup analyses for each category were based on (healthy or unhealthy), dose of supplement (>200 or <200), duration of intervention (>5weeks or <5 weeks), (diabetic or non-diabetic patients) and (medicine use or no medicine use). By doing subgroup analysis, we found that none of the mentioned factors was the source of heterogeneity.

The present meta-analysis faced several limitations. Some studies included in this meta-analysis had not been specifically designed to assess the association between Co-Q10 and diabetes biomarkers and this relationship had been reported as an accessory finding. It should be noted that the initial concentration of HbA1c, fasting blood glucose and fasting insulin differed in each study. Moreover, sample size may also be an important factor. Indeed, a small sample size may not detect improvements in HbA1c. However, this meta-analysis has several strengths. RCTs are the most appropriate study designs to show casual effects and meta-analysis of their results can lead to a more reliable conclusion. Furthermore, we analyzed the effect of Co-Q10 on different diabetes biomarkers like fasting blood glucose, HbA1c and fasting insulin. In addition, we conducted a comprehensive search to find all the relevant articles in this field. Moreover, we considered different sources of heterogeneity.

In conclusion, our meta-analysis on clinical trials revealed that Co-Q10 supplementation slightly but significantly reduced fasting blood glucose, but not fasting insulin and HbA1c. There were many heterogeneity sources in this meta-analysis. Subgroup analysis could not remove the heterogeneity among studies. Further studies should be conducted to assess all diabetes biomarkers in the same situation.

Disclosure statement

Authors have nothing to disclose.

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References

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. 2011; 94(3): 311 – 321.
2. Arredondo A. Diabetes: a global challenge with high economic burden for public health systems and society. *Am J Public Health*. 2013; 103(2): e1 – e2.
3. Ruhe RC, McDonald RB. Use of antioxidant nutrients in the prevention and treatment of type 2 diabetes. *J Am Coll Nutr*. 2001; 20(5 Suppl): 363S – 369S.
4. Robertson RP. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *J Biol Chem*. 2004; 279(41): 42351 – 42354.
5. Kalen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids*. 1990; 24(7): 579 – 584.
6. Watts G, Playford D, Croft K, Ward N, Mori T, Burke V. Coenzyme Q10 improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. *Diabetologia*. 2002; 45(3): 420 – 426.
7. Shekelle P, Morton S, Hardy ML. Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease. *Evid Rep Technol Assess (Summ)*. 2003; (83): 1 – 3.
8. Stocker R, Bowry WV, Frei B. Ubiquinol-10 protects human low References density lipoprotein more efficiently against lipid peroxidation than does alphatocopherol. *Proc Natl Acad Sci U S A*. 1991; 88(5): 1646 – 1650.
9. Kishi T, Kishi H, Watanabe T, Folkers K. Bioenergetics in clinical medicine. XI. Studies on coenzyme Q and diabetes mellitus. *J Med*. 1975; 7(3–4): 307 – 321.
10. Shimura Y, Hogimoto S. Significance of coenzyme Q10 on the treatment of diabetes mellitus. *Jpn J Clin Exp Med*. 1981; 58(1): 349 –352.
11. McCarty MF. Maturity-onset diabetes mellitus—toward a physiologically appropriate management. *Med Hypotheses*. 1981; 7(10): 1265 – 1285.
12. Lim SC, Tan HH, Goh SK, Subramaniam T, Sum CF, Tan IK, et al.

Oxidative burden in prediabetic and diabetic individuals: evidence from plasma coenzyme Q10. *Diabet Med*. 2006; 23(12): 1344 – 1349.
13. Singh R, Niaz M, Rastogi S, Shukla P, Thakur A. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. *J Hum Hypertens*. 1999; 13(3): 203 – 208.
14. Eriksson J, Forsen T, Mortensen S, Rohde M. The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. *Biofactors*. 1999; 9(2–4): 315 – 318.
15. Henriksen JE, Andersen CB, Hother-Nielsen O, Vaag A, Mortensen SA, Beck-Nielsen H. Impact of ubiquinone (coenzyme Q10) treatment on glycaemic control, insulin requirement and well-being in patients with Type 1 diabetes mellitus. *Diabet Med*. 1999; 16(4): 312 – 318.
16. Lipsey MW, Wilson DB. *Practical Meta-analysis*. Sage publications, Thousand Oaks, CA, 2001.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21(11): 1539 – 1558.
18. Cao Y, Xu Y, Lu T, Gao F, Mo Z. Metan: fixed- and random-effects meta-analysis. *Stata J*. 2008; 8(3–4): 3 – 28.
19. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ*. 2007; 176(8): 1091 – 1096.
20. Playford DA, Watts GF, Croft KD, Burke V. Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type 2 diabetes. *Atherosclerosis*. 2003; 168(1): 169-79.
21. Singh RB, Niaz MA. Serum concentration of lipoprotein (a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role. *Int J Cardiol*. 1999; 68(1): 23 – 29.
22. Ikematsu H, Nakamura K, Harashima S-i, Fujii K, Fukutomi N. Safety assessment of coenzyme Q10 (Kaneka Q10) in healthy subjects: a double-blind, randomized, placebo-controlled trial. *Regul Toxicol Pharmacol*. 2006; 44(3): 212 – 218.
23. Shargorodsky M, Debby O, Matas Z, Zimlichman R. Research Effect of long-term treatment with antioxidants (vitamin C, vitamin E, coenzyme Q10 and selenium) on arterial compliance, humoral factors and inflammatory markers in patients with multiple cardiovascular risk factors. *Nutr Metab (Lond)*. 2010; 7: 55.
24. Hamilton SJ, Chew GT, Watts GF. Coenzyme Q10 improves endothelial dysfunction in statin-treated type 2 diabetic patients. *Diabetes Care*. 2009; 32(5): 810 – 812.
25. Hodgson J, Watts G, Playford D, Burke V, Croft K. Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr*. 2002; 56(11): 1137 – 1142.
26. Mohammed-Jawad NK, Al-Sabbagh M. Role of L-carnitine and Coenzyme Q10 as Adjuvant Therapy in Patients with Type 2 Diabetes Mellitus. *Eur J Clin Nutr*. 2014; 2: 82 – 86.
27. Yubero-Serrano EM, Delgado-Casado N, Delgado-Lista J, Perez-Martinez P, Tasset-Cuevas I, Santos-Gonzalez M, et al. Postprandial antioxidant effect of the Mediterranean diet supplemented with coenzyme Q10 in elderly men and women. *Age(Dordr)*. 2011; 33(4): 579 – 590.
28. Chew GT, Watts GF, Davis TM, Stuckey BG, Beilin LJ, Thompson PL, et al. Hemodynamic effects of fenofibrate and coenzyme Q10 in type 2 diabetic subjects with left ventricular diastolic dysfunction. *Diabetes Care*. 2008; 31(8): 1502 – 1509.
29. Mori TA, Burke V, Puddey IB, Irish AB, Cowpland CA, Beilin LJ, et al. The effects of ω3 fatty acids and coenzyme Q10 on blood pressure and heart rate in chronic kidney disease: a randomized controlled trial. *J Hypertens*. 2009; 27(9): 1863 – 1872.
30. Dai YL, Luk TH, Yiu KH, Wang M, Yip PM, Lee SW, et al. Reversal of mitochondrial dysfunction by coenzyme Q10 supplement improves endothelial function in patients with ischaemic left ventricular systolic dysfunction: a randomized controlled trial. *Atherosclerosis*. 2011; 216(2): 395 – 401.
31. Kolahdouz Mohammadi R, Hosseinzadeh-Attar MJ, Eshraghian MR, Nakhjavani M, Khorami E, Esteghamati A. The effect of coenzyme Q10 supplementation on metabolic status of type 2 diabetic patients. *Minerva Gastroenterol Dietol*. 2013; 59(2): 231 – 236.
32. Folkers K, Littarru GP, Yamagami T. Coenzyme Q10, alpha-tocopherol, and free cholesterol levels in sera from diabetic patients. *Biomedical and Clinical Aspects of Coenzyme Q*. Amsterdam: Elsevier Science publisher; 1991: 151 – 158.
33. Menke T, Niklowitz P, Wiesel T, Andler W. Antioxidant level and redox status of coenzyme Q10 in the plasma and blood cells of children with diabetes mellitus type 1. *Pediatr Diabetes*. 2008; 9(6): 540 – 545.
34. Wahlquist ML, Wattanapenparboon N, Sarige GS, Kannar D. Bioavailability of two different formulations of coenzyme Q10 in healthy subjects. *Asia Pac J Clin Nutr*. 1998; 7(1): 37 – 40
35. Yamagami T, Shibata N, Folkers K. Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension. *Res Commun Chem Pathol Pharmacol*. 1975; 11(2): 273 – 288.
36. Digiesi V, Cantini F, Oradei A, Bisi G, Guarino G, Brocchi A, et al. Coenzyme Q10 in essential hypertension. *Mol Aspects Med*. 1994; 15 Suppl: 257 – 263.
37. Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. *South Med J*. 2001; 94(11): 1112 – 1117.
38. Bonnefont-Rousselot D, Bastard JP, Jaudon MC, Delattre J. Consequences of the diabetic status on the oxidant/antioxidant balance. *Diabetes Metab*. 2000; 26(3): 163 – 177.
39. West IC. Radicals and oxidative stress in diabetes. *Diabet Med*. 2000; 17(4): 171 – 180.
40. McCarty MF. Can correction of sub-optimal coenzyme Q status improve b-cell function in type II diabetics? *Med Hypotheses*. 1999; 52(5): 397 – 400.
41. Ceriello A. Oxidative stress and glycemic regulation. *Metabolism*. 2000; 49(2 Suppl 1): 27 – 29.